

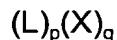
WHAT IS CLAIMED IS:

1. A multibinding compound comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers, which may be the same or different, each of said ligands comprising a ligand domain capable of binding to a Ca<sup>++</sup> channel.
2. A multibinding compound according to Claim 1, wherein the ligands are selected from A-53930A, AE-0047, AGN-190604, AGN-190744, AH-1058, AHR-12742, AHR-16303B, AHR-16462B, AIT-110, AIT-111, AJ-3941, AM-336, amlopidine (including S-(-), R-(+), and racemic), anipamil, AP-1067, aranidipine, atosiban, azelnidipine, barnidipine, Bay-t-7207, Bay-y-5959, Bay-z-4406, BBR-2160, belfosdil, BIII-890-CL, bisaramil, BMS-181102, BMS-188107, BMY-43011, BRL-32872, buflomedil, CD-349, CD-832, CERM-12816, CGR-28932, cilnidipine, clentiazem, clevidipine, CNS-1067, CNS-1237, CNS-2103, CP-060S, CPC-301, CPC-317, CPU-86017, D-2024, darodipine, DHP-218, diltiazem, diperidipine, dopropidil, dotarazine, dronedarone, DTZ-323, E-047/1, efonidipine, EGIS-7229, elgodipine, emopamil, etomoxir, F-0401, fantofarone, fasudil, FCE-24265, FCE-26262, FCE-27335, FCE-27892, FCE-28718, felodipine, FPL-64176, FR-172516, FRG-8701, furnidipine, GS-386, iganidipine, ipenozazone, isradipine, JTV-591, KP-840, KT-362, L-366682, lacidipine, LAS-0538, LCB-2514, lemildipine, lercanidipine, leualacin, lifarizine, LOE-908, lomerizine, lubeluzole, LY-042826, manidipine, McN-6186, mibefradil, monatepil, MR-14134, N-3601, NCC-1048, nefiracetam, nexopamil, nifedipine, nifedipine, Nifelan, nilvadipine, nimodipine, NNC-09-0026, NPS-568, NS-638, NS-649, NS-696, NS-7, OPC-8490, Org-13061, Org-30029, oxodipine, P-5, palonidipine, PCA-50922, PCA-50938, PCA-50941, PD-029361, PD-157667, PD-158143, PD-176078, pranidipine, QX-314, ranolazine, RHG-

2716, RingCap, Ro-11-2933, RS-5773, RU-43945, RWJ-22108,  
RWJ-22726, RWJ-29009, RWJ-37868, S-12968, S-2150, S-312-d, SANK-  
71996, SB-201823, SB-206284A, SB-23736, SD-3212, semotiadil, SIB-  
1281, siratiazem, SKF-45675, SKF-96365, SKT-M-26, SL-34.0829, SL-  
5 87.0495, SM-6586, SNX-124, SNX-236, SNX-239, SNX-325, SNX-482, SQ-  
31727, SQ-33351, SQ-34399, SR-33805, TA-993, tamolarizine, TDN-345,  
temiverine, terodiline, TH-9229, TN-871, U-88999, U-92032, U-92798, UCL-  
1439, UK-1656, UK-55444, UK-56593, UK-84149, verapamil, Verelan,  
vexibinol, VUF-8929, WAY-141520, XB-513, XT-044, Y-22516, YH-334,  
10 YM-1615-4, YM-430, Z-6568, zatebradine, ziconotide, and ZM-224832.

3. A multibinding compound according to claim 2, wherein the ligands  
are selected from the group consisting of verapamil, diltiazem, benziazem  
clentiazem, nicardipine, nifedipine, nilvadipine, nitredipine, nimodipine,  
isradipine, lacidipine, amlodipine, nisoldipine, isradipine, mibefrodil,  
15 amlodipine, felodipine, nimodipine, bepridil, SQ 32,910 and SQ 32,428.

4. A multibinding compound represented by Formula I:



|

20 where each L is a ligand that may be the same or different at each  
occurrence;  
X is a linker that may be the same or different at each occurrence;  
p is an integer of from 2 to 10; and  
q is an integer of from 1 to 20;  
25 wherein each of said ligands comprises a ligand domain capable of binding  
to a  $Ca^{++}$  channel.

5. A multibinding compound according to Claim 4, wherein  $q$  is less than  $p$ .

6. A multibinding compound according to Claim 4, wherein the ligands are selected from A-53930A, AE-0047, AGN-190604, AGN-190744, AH-5 1058, AHR-12742, AHR-16303B, AHR-16462B, AIT-110, AIT-111, AJ-3941, AM-336, amlopidine (including S-(-), R-(+), and racemic), anipamil, AP-1067, aranidipine, atosiban, azelnidipine, barnidipine, Bay-t-7207, Bay-y-5959, Bay-z-4406, BBR-2160, belfosdil, BIII-890-CL, bisaramil, BMS-181102, BMS-188107, BMY-43011, BRL-32872, buflomedil, CD-349, CD-10 832, CERM-12816, CGP-28932, cilnidipine, clentiazem, clevidipine, CNS-1067, CNS-1237, CNS-2103, CP-060S, CPC-301, CPC-317, CPU-86017, D-2024, darodipine, DHP-218, diltiazem, diperidipine, dpropidil, dotarazine, dronedarone, DTZ-323, E-047/1, efondipine, EGIS-7229, elgodipine, emopamil, etomoxir, F-0401, fantofarone, fasudil, FCE-24265, FCE-26262, 15 FCE-27335, FCE-27892, FCE-28718, felodipine, FPL-64176, FR-172516, FRG-8701, fumidipine, GS-386, iganidipine, ipenozazone, isradipine, JTV-591, KP-840, KT-362, L-366682, lacidipine, LAS-0538, LCB-2514, lemildipine, lercanidipine, leualacin, lifarizine, LOE-908, lomerizine, lubeluzole, LY-042826, manidipine, McN-6186, mibefradil, monatepil, MR-20 14134, N-3601, NCC-1048, nefiracetam, nexopamil, nifedipine, nifedipine, Nifelan, nilvadipine, nimodipine, NNC-09-0026, NPS-568, NS-638, NS-649, NS-696, NS-7, OPC-8490, Org-13061, Org-30029, oxodipine, P-5, palonidipine, PCA-50922, PCA-50938, PCA-50941, PD-029361, PD-157667, PD-158143, PD-176078, pranidipine, QX-314, ranolazine, RHG-25 2716, RingCap, Ro-11-2933, RS-5773, RU-43945, RWJ-22108, RWJ-22726, RWJ-29009, RWJ-37868, S-12968, S-2150, S-312-d, SANK-71996, SB-201823, SB-206284A, SB-23736, SD-3212, semotiadil, SIB-

1281, siratiazem, SKF-45675, SKF-96365, SKT-M-26, SL-34.0829, SL-  
87.0495, SM-6586, SNX-124, SNX-236, SNX-239, SNX-325, SNX-482, SQ-  
31727, SQ-33351, SQ-34399, SR-33805, TA-993, tamolarizine, TDN-345,  
temiverine, terodilane, TH-9229, TN-871, U-88999, U-92032, U-92798, UCL-  
5 1439, UK-1656, UK-55444, UK-56593, UK-84149, verapamil, Verelan,  
vexibinol, VUF-8929, WAY-141520, XB-513, XT-044, Y-22516, YH-334,  
YM-1615-4, YM-430, Z-6568, zatebradine, ziconotide, and ZM-224832.

7. A multibinding compound according to claim 6, wherein the ligands  
are selected from the group consisting of verapamil, diltiazem, benziazem  
10 clentiazem, nicardipine, nifedipine, nilvadipine, nitredipine, nimodipine,  
isradipine, lacidipine, amlodipine, nisoldipine, isradipine, mibefrodil,  
amlodipine, felodipine, nimodipine, bepridil, SQ 32,910 and SQ 32,428.

8. The multibinding compound of Claim 4, wherein the linker is is  
represented by the following formula:

15  $-X'-Z-(Y'-Z)_m-Y'-Z-X'$

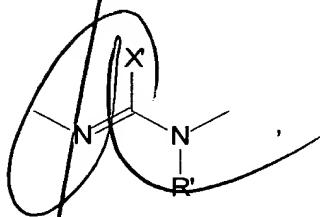
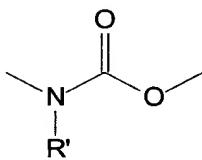
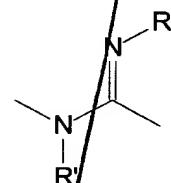
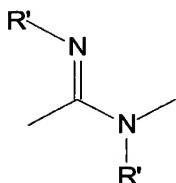
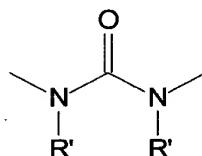
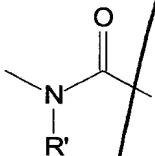
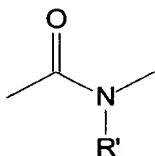
in which:

m is an integer of from 0 to 20;

X' at each separate occurrence is -O-, -S-, -S(O)-, -S(O)<sub>2</sub>-, -NR-, -N<sup>+</sup> R R'-,  
-C(O)-, -C(O)O-, -C(O)NH-, -C(S), -C(S)O-, -C(S)NH- or a covalent bond,  
20 where R and R' at each separate occurrence are as defined below for R'  
and R'";

Z is at each separate occurrence selected from alkylene, substituted  
alkylene, alkylalkoxy, cycloalkylene, substituted cycloalkylene, alkenylene,  
substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene,  
25 substituted alkenylene, arylene, substituted arylene, heteroarylene,  
heterocylene, substituted heterocylene, crown compounds, or a covalent  
bond;

Y' and Y' at each separate occurrence are selected from -S-S- or a covalent bond;



in which:

n is 0, 1 or 2; and

5 R' and R'' at each separate occurrence are selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl or heterocyclic.

9. The multibinding compound of Claim 8 wherein p is 2 and q is 1.

10. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more multibinding compounds, or pharmaceutically acceptable salts thereof, comprising 2 to 10 ligands which may be the same or different and which

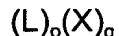
are covalently attached to a linker or linkers, which may be the same or different, each of said ligands comprising a ligand domain capable of binding to a Ca<sup>++</sup> channel of a cell mediating mammalian diseases or conditions, thereby modulating the diseases or conditions.

5 11. A pharmaceutical composition according to Claim 10, wherein the ligands are selected from A-53930A, AE-0047, AGN-190604, AGN-190744, AH-1058, AHR-12742, AHR-16303B, AHR-16462B, AIT-110, AIT-111, AJ-3941, AM-336, amlopidine (including S-(-), R-(+), and racemic), anipamil, AP-1067, aranidipine, atosiban, azelnidipine, barnidipine, Bay-t-7207, Bay-10 y-5959, Bay-z-4406, BBR-2160, belfosdil, BIII-890-CL, bisaramil, BMS-181102, BMS-188107, BMY-43011, BRL-32872, buflomedil, CD-349, CD-832, CERM-12816, CGRP28932, cilnidipine, clentiazem, clevidipine, CNS-1067, CNS-1237, CNS-2103, CP-060S, CPC-301, CPC-317, CPU-86017, D-2024, darodipine, DHP-218, diltiazem, diperidipine, dopropidil, dotarazine, 15 dronedarone, DTZ-323, E-047/1, efonidipine, EGIS-7229, elgodipine, emopamil, etomoxir, F-0401, fantofarone, fasudil, FCE-24265, FCE-26262, FCE-27335, FCE-27892, FCE-28718, felodipine, FPL-64176, FR-172516, FRG-8701, furnidipine, GS-386, iganidipine, ipenozazone, isradipine, JTV-591, KP-840, KT-362, L-366682, lacidipine, LAS-0538, LCB-2514, 20 lemildipine, lercanidipine, leualacin, lifarizine, LOE-908, lomerizine, lubeluzole, LY-042826, manidipine, McN-6186, mibefradil, monatepil, MR-14134, N-3601, NCC-1048, nefiracetam, nexopamil, nifedipine, nifedipine, Nifelan, nilvadipine, nimodipine, NNC-09-0026, NPS-568, NS-638, NS-649, NS-696, NS-7, OPC-8490, Org-13061, Org-30029, oxodipine, P-5, 25 palonidipine, PCA-50922, PCA-50938, PCA-50941, PD-029361, PD-157667, PD-158143, PD-176078, pranidipine, QX-314, ranolazine, RHG-2716, RingCap, Ro-11-2933, RS-5773, RU-43945, RWJ-22108, RWJ-22726, RWJ-29009, RWJ-37868, S-12968, S-2150, S-312-d, SANK-

71996, SB-201823, SB-206284A, SB-23736, SD-3212, semotiadil, SIB-1281, siratiazem, SKF-45675, SKF-96365, SKT-M-26, SL-34.0829, SL-87.0495, SM-6586, SNX-124, SNX-236, SNX-239, SNX-325, SNX-482, SQ-31727, SQ-33351, SQ-34399, SR-33805, TA-993, tamolarizine, TDN-345, 5 temiverine, terodilane, TH-9229, TN-871, U-88999, U-92032, U-92798, UCL-1439, UK-1656, UK-55444, UK-56593, UK-84149, verapamil, Verelan, vexibinol, VUF-8929, WAY-141520, XB-513, XT-044, Y-22516, YH-334, YM-1615-4, YM-430, Z-6568, zatebradine, ziconotide, and ZM-224832.

12. A pharmaceutical composition according to claim 11, wherein the 10 ligands are selected from the group consisting of verapamil, diltiazem, benziazem clentiazem, nicardipine, nifedipine, nilvadipine, nitredipine, nimodipine, isradipine, lacidipine, amlodipine, nisoldipine, isradipine, mibefrodil, amlodipine, felodipine, nimodipine, bepridil, SQ 32,910 and SQ 32,428.

15 13. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more multibinding compounds represented by Formula I,



|

20 and pharmaceutically acceptable salts thereof, where each L is a ligand that may be the same or different at each occurrence;

X is a linker that may be the same or different at each occurrence;

p is an integer of from 2 to 10; and

25 q is an integer of from 1 to 20;

wherein each of said ligands comprises a ligand domain capable of binding to a Ca<sup>++</sup> channel of a cell mediating mammalian diseases or conditions, thereby modulating the diseases or conditions.

14. A pharmaceutical composition according to Claim 4, wherein the

5 ligands are selected from A-53930A, AE-0047, AGN-190604, AGN-190744, AH-1058, AHR-12742, AHR-16303B, AHR-16462B, AIT-110, AIT-111, AJ-3941, AM-336, amlopidine (including S-(-), R-(+), and racemic), anipamil, AP-1067, aranidipine, atosiban, azelnidipine, barnidipine, Bay-t-7207, Bay-y-5959, Bay-z-4406, BBR-2160, belfosdil, BIII-890-CL, bisaramil, BMS-10 181102, BMS-188107, BMY-43011, BRL-32872, buflomedil, CD-349, CD-832, CERM-12816, CGP-28932, cilnidipine, clentiazem, clevidipine, CNS-1067, CNS-1237, CNS-2103, CP-060S, CPC-301, CPC-317, CPU-86017, D-2024, darodipine, DHP-218, diltiazem, diperidipine, dopropidil, dotarazine, dronedarone, DTZ-323, E-047/1, efondipine, EGIS-7229, elgodipine,

15 emopamil, etomoxir, F-0401, fantofarone, fasudil, FCE-24265, FCE-26262, FCE-27335, FCE-27892, FCE-28718, felodipine, FPL-64176, FR-172516, FRG-8701, furnidipine, GS-386, iganidipine, ipenozazone, isradipine, JTV-591, KP-840, KT-362, L-366682, lacidipine, LAS-0538, LCB-2514, lemildipine, lercanidipine, leualacin, lifarizine, LOE-908, lomerizine,

20 lubeluzole, LY-042826, manidipine, McN-6186, mibefradil, monatepil, MR-14134, N-3601, NCC-1048, nefiracetam, nexopamil, nifedipine, nifedipine, Nifelan, nilvadipine, nimodipine, NNC-09-0026, NPS-568, NS-638, NS-649, NS-696, NS-7, OPC-8490, Org-13061, Org-30029, oxodipine, P-5, palonidipine, PCA-50922, PCA-50938, PCA-50941, PD-029361, PD-25 157667, PD-158143, PD-176078, pranidipine, QX-314, ranolazine, RHG-2716, RingCap, Ro-11-2933, RS-5773, RU-43945, RWJ-22108, RWJ-22726, RWJ-29009, RWJ-37868, S-12968, S-2150, S-312-d, SANK-71996, SB-201823, SB-206284A, SB-23736, SD-3212, semotiadil, SIB-

1281, siratiazem, SKF-45675, SKF-96365, SKT-M-26, SL-34.0829, SL-  
87.0495, SM-6586, SNX-124, SNX-236, SNX-239, SNX-325, SNX-482, SQ-  
31727, SQ-33351, SQ-34399, SR-33805, TA-993, tamolarizinè, TDN-345,  
temiverine, terodilane, TH-9229, TN-871, U-88999, U-92032, U-92798, UCL-  
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vexibinol, VUF-8929, WAY-141520, XB-513, XT-044, Y-22516, YH-334,  
YM-1615-4, YM-430, Z-6568, zatebradine, ziconotide, and ZM-224832.

15. A pharmaceutical composition according to claim 6, wherein the  
ligands are selected from the group consisting of verapamil, diltiazem,  
10 benziazem clentiazem, nicardipine, nifedipine, nilvadipine, nitredipine,  
nimodipine, isradipine, lacidipine, amlodipine, nisoldipine, isradipine,  
mibefrodil, amlodipine, felodipine, nimodipine, bepridil, SQ 32,910 and SQ  
32,428.

16. A method for modulating the activity of a  $\text{Ca}^{++}$  channel in a biologic  
15 tissue, which method comprises contacting a tissue having a  $\text{Ca}^{++}$  channel  
with a multibinding compound, or a pharmaceutically acceptable salt thereof,  
under conditions sufficient to produce a change in the activity of the channel  
in said tissue, wherein the multibinding compound comprises 2 to 10 ligands  
which may be the same or different and which are covalently attached to a  
20 linker or linkers, which may be the same or different, each of said ligands  
comprising a ligand domain capable of binding to a  $\text{Ca}^{++}$  channel.

17. A method according to Claim 16, wherein the ligands are selected  
from A-53930A, AE-0047, AGN-190604, AGN-190744, AH-1058, AHR-  
12742, AHR-16303B, AHR-16462B, AIT-110, AIT-111, AJ-3941, AM-336,  
25 amlopidine (including S-(-), R-(+), and racemic), anipamil, AP-1067,  
aranidipine, atosiban, azelnidipine, barnidipine, Bay-t-7207, Bay-y-5959,

Bay-z-4406, BBR-2160, belfosdil, BIII-890-CL, bisaramil, BMS-181102, BMS-188107, BMY-43011, BRL-32872, buflomedil, CD-349, CD-832, CERM-12816, CGP-28932, cilnidipine, clentiazem, clevidipine, CNS-1067, CNS-1237, CNS-2103, CP-060S, CPC-301, CPC-317, CPU-86017, D-2024, 5 darodipine, DHP-218, diltiazem, diperidipine, dopropidil, dotarazine, dronedarone, DTZ-323, E-047/1, efondipine, EGIS-7229, elgodipine, emopamil, etomoxir, F-0401, fantofarone, fasudil, FCE-24265, FCE-26262, FCE-27335, FCE-27892, FCE-28718, felodipine, FPL-64176, FR-172516, FRG-8701, furnidipine, GS-386, iganidipine, ipenozazone, isradipine, JTV- 10 591, KP-840, KT-362, L-366682, lacidipine, LAS-0538, LCB-2514, lemildipine, lercanidipine, leualacin, lifarizine, LOE-908, lomerizine, lubeluzole, LY-042826, manidipine, McN-6186, mibefradil, monatepil, MR- 14134, N-3601, NCC-1048, nefiracetam, nexopamil, nifedipine, nifedipine, Nifelan, nilvadipine, nimodipine, NNC-09-0026, NPS-568, NS-638, NS-649, 15 NS-696, NS-7, OPC-8490, Org-13061, Org-30029, oxodipine, P-5, palonidipine, PCA-50922, PCA-50938, PCA-50941, PD-029361, PD- 157667, PD-158143, PD-176078, pranidipine, QX-314, ranolazine, RHG- 2716, RingCap, Ro-11-2933, RS-5773, RU-43945, RWJ-22108, RWJ-22726, RWJ-29009, RWJ-37868, S-12968, S-2150, S-312-d, SANK- 20 71996, SB-201823, SB-206284A, SB-23736, SD-3212, semotiadil, SIB- 1281, siratiazem, SKF-45675, SKF-96365, SKT-M-26, SL-34.0829, SL- 87.0495, SM-6586, SNX-124, SNX-236, SNX-239, SNX-325, SNX-482, SQ- 31727, SQ-33351, SQ-34399, SR-33805, TA-993, tamolarizine, TDN-345, temiverine, terodilane, TH-9229, TN-871, U-88999, U-92032, U-92798, UCL- 25 1439, UK-1656, UK-55444, UK-56593, UK-84149, verapamil, Verelan, vexibinol, VUF-8929, WAY-141520, XB-513, XT-044, Y-22516, YH-334, YM-1615-4, YM-430, Z-6568, zatebradine, ziconotide, and ZM-224832.

18. A method according to claim 17, wherein the ligands are selected from the group consisting of verapamil, diltiazem, benziazem clentiazem, nicardipine, nifedipine, nilvadipine, nitredipine, nimodipine, isradipine, lacidipine, amlodipine, nisoldipine, isradipine, mibefrodil, amlodipine, 5 felodipine, nimodipine, bepridil, SQ 32,910 and SQ 32,428.

19. A method for treating a disease or condition in a mammal resulting from an activity of a  $\text{Ca}^{++}$  channel, which method comprises administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and one or 10 more multibinding compounds, or pharmaceutically acceptable salts thereof, comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers, which may be the same or different, each of said ligands comprising a ligand domain capable of binding to a  $\text{Ca}^{++}$  channel of a cell mediating mammalian diseases or 15 conditions.

20. A method according to Claim 19, wherein the ligands are selected from A-53930A, AE-0047, AGN-190604, AGN-190744, AH-1058, AHR-12742, AHR-16303B, AHR-16462B, AIT-110, AIT-111, AJ-3941, AM-336, amlopidine (including S-(-), R-(+), and racemic), anipamil, AP-1067, 20 aranidipine, atosiban, azelnidipine, barnidipine, Bay-t-7207, Bay-y-5959, Bay-z-4406, BBR-2160, belfosdil, BIII-890-CL, bisaramil, BMS-181102, BMS-188107, BMY-43011, BRL-32872, buflomedil, CD-349, CD-832, CERM-12816, CGP-28932, cilnidipine, clentiazem, clevidipine, CNS-1067, CNS-1237, CNS-2103, CP-060S, CPC-301, CPC-317, CPU-86017, D-2024, 25 darodipine, DHP-218, diltiazem, diperdipine, dopropidil, dotarazine, dronedarone, DTZ-323, E-047/1, efonidipine, EGIS-7229, elgodipine, emopamil, etomoxir, F-0401, fantofarone, fasudil, FCE-24265, FCE-26262,

FCE-27335, FCE-27892, FCE-28718, felodipine, FPL-64176, FR-172516, FRG-8701, furnidipine, GS-386, iganidipine, ipenozazone, isradipine, JTV-591, KP-840, KT-362, L-366682, lacidipine, LAS-0538, LCB-2514, lemildipine, lercanidipine, leualacin, lifarizine, LOE-908, lomerizine,  
5 lubeluzole, LY-042826, manidipine, McN-6186, mibefradil, monatepil, MR-14134, N-3601, NCC-1048, nefiracetam, nexopamil, nifedipine, nifedipine, Nifelan, nilvadipine, nimodipine, NNC-09-0026, NPS-568, NS-638, NS-649, NS-696, NS-7, OPC-8490, Org-13061, Org-30029, oxodipine, P-5, palonidipine, PCA-50922, PCA-50938, PCA-50941, PD-029361, PD-  
10 157667, PD-158143, PD-176078, pranidipine, QX-314, ranolazine, RHG-2716, RingCap, Ro-11-2933, RS-5773, RU-43945, RWJ-22108, RWJ-22726, RWJ-29009, RWJ-37868, S-12968, S-2150, S-312-d, SANK-71996, SB-201823, SB-206284A, SB-23736, SD-3212, semotiadil, SIB-1281, siratiazem, SKF-45675, SKF-96365, SKT-M-26, SL-34.0829, SL-  
15 87.0495, SM-6586, SNX-124, SNX-236, SNX-239, SNX-325, SNX-482, SQ-31727, SQ-33351, SQ-34399, SR-33805, TA-993, tamolarizine, TDN-345, temiverine, terodiline, TH-9229, TN-871, U-88999, U-92032, U-92798, UCL-1439, UK-1656, UK-55444, UK-56593, UK-84149, verapamil, Verelan, vexibinol, VUF-8929, WAY-141520, XB-513, XT-044, Y-22516, YH-334,  
20 YM-1615-4, YM-430, Z-6568, zatebradine, ziconotide, and ZM-224832.

21. A method according to claim 20, wherein the ligands are selected from the group consisting of verapamil, diltiazem, benziazem clentiazem, nicardipine, nifedipine, nilvadipine, nitredipine, nimodipine, isradipine, lacidipine, amlodipine, nisoldipine, isradipine, mibefradil, amlodipine, felodipine, nimodipine, bepridil, SQ 32,910 and SQ 32,428.  
25

22. A method for treating a disease or condition in a mammal resulting from an activity of a  $\text{Ca}^{++}$  channel, which method comprises administering to

said mammal a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and one or more multibinding compounds represented by Formula I,

$(L)_p(X)_q$

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I

and pharmaceutically acceptable salts thereof,  
where each L is a ligand that may be the same or different at each occurrence;  
X is a linker that may be the same or different at each occurrence;  
10 p is an integer of from 2 to 10; and  
q is an integer of from 1 to 20;  
wherein each of said ligands comprises a ligand domain capable of binding to a  $Ca^{++}$  channel of a cell mediating mammalian diseases or conditions.

23. A method according to Claim 22, wherein the ligands are selected  
15 from A-53930A, AE-0047, AGN-190604, AGN-190744, AH-1058, AHR-  
12742, AHR-16303B, AHR-16462B, AIT-110, AIT-111, AJ-3941, AM-336,  
amlopidine (including S-(-), R-(+), and racemic), anipamil, AP-1067,  
aranidipine, atosiban, azelnidipine, barnidipine, Bay-t-7207, Bay-y-5959,  
Bay-z-4406, BBR-2160, belfosdil, BIII-890-CL, bisaramil, BMS-181102,  
20 BMS-188107, BMY-43011, BRL-32872, buflomedil, CD-349, CD-832,  
CERM-12816, CGP-28932, cilnidipine, clentiazem, clevidipine, CNS-1067,  
CNS-1237, CNS-2103, CP-060S, CPC-301, CPC-317, CPU-86017, D-2024,  
darodipine, DHP-218, diltiazem diperidipine, dopropidil, dotarazine,  
dronedarone, DTZ-323, E-047/1, efonidipine , EGIS-7229, elgodipine,  
25 emopamil, etomoxir, F-0401, fantofarone, fasudil, FCE-24265, FCE-26262,  
FCE-27335, FCE-27892, FCE-28718, felodipine, FPL-64176, FR-172516,

FRG-8701, furnidipine, GS-386, iganidipine, ipenoxazone, isradipine, JTV-591, KP-840, KT-362, L-366682, lacidipine, LAS-0538, LCB-2514, lemildipine, lercanidipine, leualacin, lifarizine, LOE-908, lomerizine, lubeluzole, LY-042826, manidipine, McN-6186, mibefradil, monatepil, MR-5 14134, N-3601, NCC-1048, nefiracetam, nexopamil, nifedipine, nifedipine, Nifelan, nilvadipine, nimodipine, NNC-09-0026, NPS-568, NS-638, NS-649, NS-696, NS-7, OPC-8490, Org-13061, Org-30029, oxodipine, P-5, palonidipine, PCA-50922, PCA-50938, PCA-50941, PD-029361, PD-10 157667, PD-158143, PD-176078, pranidipine, QX-314, ranolazine, RHG-2716, RingCap, Ro-11-2933, RS-5773, RU-43945, RWJ-22108, RWJ-22726, RWJ-29009, RWJ-37868, S-12968, S-2150, S-312-d, SANK-71996, SB-201823, SB-206284A, SB-23736, SD-3212, semotiadil, SIB-1281, siratiazem, SKF-45675, SKF-96365, SKT-M-26, SL-34.0829, SL-87.0495, SM-6586, SNX-124, SNX-236, SNX-239, SNX-325, SNX-482, SQ-15 31727, SQ-33351, SQ-34399, SR-33805, TA-993, tamolarizine, TDN-345, temiverine, terodiline, TH-9229, ~~TN-871~~, U-88999, U-92032, U-92798, UCL-1439, UK-1656, UK-55444, UK-56593, UK-84149, verapamil, Verelan, vexibinol, VUF-8929, WAY-141520, XB-513, XT-044, Y-22516, YH-334, YM-1615-4, YM-430, Z-6568, zatebradine, ziconotide, and ZM-224832.

20 24. A method according to claim 23, wherein the ligands are selected from the group consisting of verapamil, diltiazem, benziazem clentiazem, nicardipine, nifedipine, nilvadipine, nitredipine, nimodipine, isradipine, lacidipine, amlodipine, nisoldipine, isradipine, mibefradil, amlodipine, felodipine, nimodipine, bepridil, SQ 32,910 and SQ 32,428.

25 25. A method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

5 (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

10 (d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

26. A method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

15 (a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

20 (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

25 (d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

27. The method according to Claim 25 or 26 wherein the preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b).

5 28. The method according to Claim 27 wherein the multimeric ligand compounds comprising the multimeric ligand compound library are dimeric.

29. The method according to Claim 28 wherein the dimeric ligand compounds comprising the dimeric ligand compound library are heterodimeric.

10 30. The method according to Claim 29 wherein the heterodimeric ligand compound library is prepared by sequential addition of a first and second ligand.

31. The method according to Claim 25 or 26 wherein, prior to procedure (d), each member of the multimeric ligand compound library is isolated from 15 the library.

32. The method according to Claim 31 wherein each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

20 33. The method according to Claim 25 or Claim 26 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and /or polarizability and amphiphilic linkers.

34. The method according to Claim 33 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

35. The method according to Claim 34 wherein the linkers are selected to 5 have different linker lengths ranging from about 2 to 100 Å.

36. The method according to Claim 25 or 26 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

37. The method according to Claim 36 wherein said reactive functionality 10 is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the 15 linker so that a covalent linkage can be formed between the linker and the ligand.

38. The method according to Claim 25 or Claim 26 wherein the multimeric ligand compound library comprises homomeric ligand compounds.

20 39. The method according to Claim 25 or Claim 26 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

40. A library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

- (a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;
- 5 (b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and
- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands
- 10 identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

41. A library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

- (a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;
- (b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and
- 15 (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

25 42. The library according to Claim 40 or Claim 41 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different

geometry, acidic linkers, basic linkers, linkers of different polarization and /or polarizability and amphiphilic linkers.

43. The library according to Claim 42 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive  
5 groups.

44. The library according to Claim 43 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100 Å.

45. The library according to Claim 40 or 41 wherein the ligand or mixture  
10 of ligands is selected to have reactive functionality at different sites on said ligands.

46. The library according to Claim 45 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates  
15 and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

47. The library according to Claim 40 or 41 wherein the multimeric ligand  
20 compound library comprises homomeric ligand compounds.

48. The library according to Claim 40 or 41 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

49. An iterative method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

(a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the

5 ligand or mixture of ligands which target a receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted

10 under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;

(b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties;

15 (c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties;

(d) evaluating what molecular constraints imparted multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;

20 (e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;

(f) evaluating what molecular constraints imparted enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

25 (g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

50. The method according to Claim 49 wherein steps (e) and (f) are repeated from 2-50 times.

51. The method according to Claim 50 wherein steps (e) and (f) are repeated from 5-50 times.

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